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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,311	06/20/2003	Eric Adam	SYR-AKT3-5001-C1	5023

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
05/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,311	ADAM ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9,12,15,18,22-28,30 and 34* is/are pending in the application.

4a) Of the above claim(s) *18,22-28,30 and 34* is/are withdrawn from consideration.

5)☒ Claim(s) *1,4,9,12 and 15* is/are allowed.

6)☒ Claim(s) *29, 31-33, 35, and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 28, 2007 has been entered.

The application has been amended as requested in the communication filed March 28, 2007. Accordingly, claims 2, 3, 5-8, 10, 11, 13, 14, 16, 17, and 19-21 have been canceled, claims 1, 9, 18, 29, 30, and 31 have been amended, and new claims 31-36 have been added. Claims 18-28, 31, and 34 remain withdrawn from further consideration.

Claims 1, 4, 9, 12, 15, 29-33, 35, and 36 are under consideration.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 32 and 33 lack antecedent bases in the specification, in particular, the phrase non-crystalline protein.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the prior Office actions mailed 4/13/06 and 9/28/06.

Claim 29 and new claim 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the prior Office action mailed 4/13/06 and 9/28/06.

In response to the above rejection, applicants amended the claims, and argue that claim 29 meets the written description requirement and cite example 13 of the written restriction guidelines.

Applicants' arguments filed 3/28/07 have been fully considered, but they are found unpersuasive. The fact pattern of example 13 and the instant application are different. Example 13 of the written restriction guidelines does not teach any crystals of any kind. Since the claims have to be interpreted in the light of the specification, the claims in example 13 can't be interpreted as directed to a crystalline composition of the

polypeptide. In contrast, the instant application teaching is focused on the structure determination of a protein that requires a crystalline form, claim 29 reads on any crystal form of the polypeptide of SEQ ID NO: 4. The amendment of the claim to add the word "soluble" does not overcome this rejection because many water-soluble proteins have been obtained in crystal forms. New claim 31 was added to this rejection because claim 31 is directed to the polypeptide consisting of residues 136-461 of SEQ ID NO: 1 in any form including solution, powder, or any crystal.

Claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35 and 36 are directed to a specific a protein consisting of residues 136-461 of SEQ ID NO: 1 and method of making, said crystal is an orthorhombic crystal in space group $P2_12_12_1$ with unit cell dimensions a = 48.36 Angstrom, b = 72.29 Angstrom, c = 94.52 Angstrom, and $\alpha = \beta = \gamma = 90$ degrees. The specification, however, does not teach such a crystal or method of obtaining said crystal. It teaches instead an orthorhombic crystal of SEQ ID NO: 4 in space group $P2_12_12_1$ with unit cell dimensions a = 48.36 Angstrom, b = 72.29 Angstrom, c = 94.52 Angstrom, and $\alpha = \beta = \gamma = 90$ degrees obtained by a micro sitting drop method under the single set of crystallization conditions cited in paragraphs 194 and 197, at pages 47 and 48 of the specification using 15% PEG MME 5000. SEQ ID NO: 4 contains four additional amino acid residues (Cys-Arg-Ser-Leu) fused to the N-terminus of a protein consisting of residues 136-461 of SEQ ID NO: 1. Thus, the protein consisting of residue 136-461 is expected to have different physical properties such as aqueous solubility and isoelectric point, and thus, is expect to crystallize under different conditions from that of SEQ ID NO: 4. The specification does not provide any correlation between the amino acid sequence and the crystallization conditions to obtain such a crystal.

Claims 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to obtaining an orthorhombic crystal of a protein consisting of residues 136-461 of SEQ ID NO: 1 in space group $P2_12_12_1$ with unit cell dimensions a = 48.36 Angstrom, b = 72.29 Angstrom, c = 94.52 Angstrom, and $\alpha = \beta = \gamma = 90$ degrees. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance

presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The specification does not teach any crystal of a protein consisting of residues 136-461. The specification provides guidance and examples in the form of an assay to crystallize the polypeptide of SEQ ID NO: 4 in an orthorhombic crystal form in space group $P2_12_12_1$ with unit cell dimensions a = 48.36 Angstrom, b = 72.29 Angstrom, c = 94.52 Angstrom, and $\alpha = \beta = \gamma = 90$ degrees. While molecular biological techniques and genetic manipulation to make any protein are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). SEQ ID NO: 4 contains four additional amino acid residues at the N-terminus of residues 136-461. The protein consisting of residues 136-461 is expected to have different physical characteristics from that of SEQ ID NO: 4 such as aquious solubility and isolelectric point that would be expected to impact the crystallization of the protein of residues 136-461 greatly. Thus, searching for a crystallization conditions for a protein the protein of consisting of residues 136-461 of SEQ ID NO: 1 to obtain an orthorhombic crystal with the specific unit cell dimension in claims 35 and that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystallization conditions for the protein consisting of residues 136-461 of SEQ ID NO: 1 and identify a crystal suitable for structure determination by X-ray the obtained crystal as suitable for structure determination is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions which would obtain a suitable crystal for structure determination in specific space group and specific unit cell dimension where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact crystallization conditions for a protein consisting of residues 136-461 that would produce the orthorhombic crystal of claim 35. Without such guidance, the experimentation left to those skilled in the art is undue.

New Matter RejectionU:

Claims 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to new matter. The language of the claims could not be found in the specification. A claim directed to a solution of the polypeptide of SEQ ID NO: 4 would be considered favorably.

Allowable Subject Matter:

Claims 1, 4, 9, 12, and 15 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656